Exceptional response and long-term disease control following severe toxicities to BRAF inhibitors in a BRAF-V600E mutated melanoma patient.

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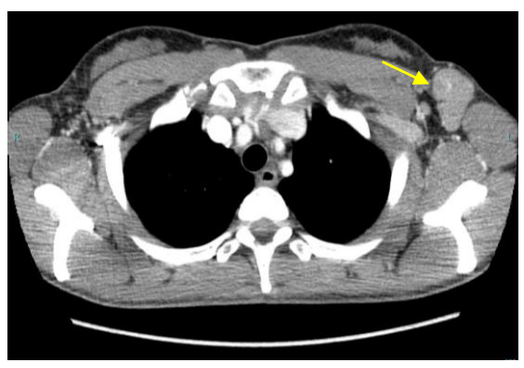
Background

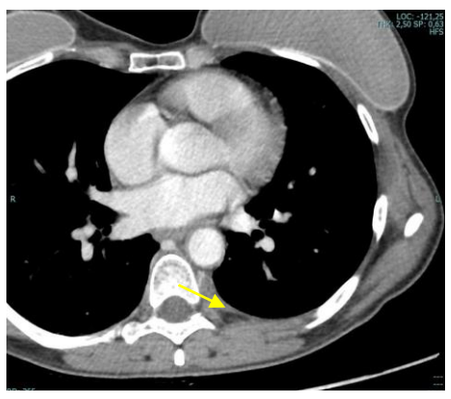
- The introduction of BRAF inhibitors radically changed the treatment landscape of BRAF V600 mutated melanoma, allowing dramatic responses and prolonging survival of melanoma patients. Nevertheless, these drugs may have a significant toxicity that may require drug interruption.
- We hereby report the case of a patient with a BRAF V600E mutated melanoma achieving a substantial response to three different BRAF inhibitors and experiencing disease control after a prolonged therapeutic pause due to toxicity.

Case description

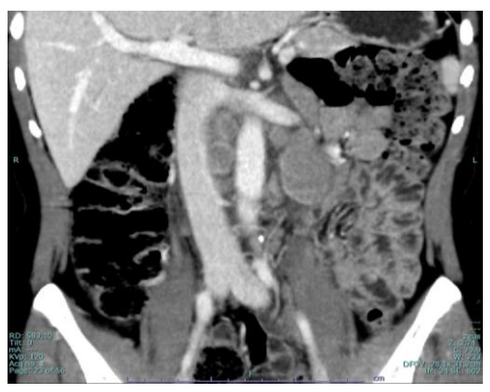
- In August 2011, a 37 years old woman underwent right axillary lymphadenectomy for a massive nodal involvement including also from a BRAF V600E mutated melanoma.
- From October 2011 to May 2014 the patient received vemurafenib single agent within a clinical trial, with no relevant toxicities and optimal disease control.
- In October 2015, a histologically confirmed left pleural relapse occurred and the patient was treated with nivolumab up to 55 courses, achieving SD as best response.
- In July 2018, the disease progressed in the pleura and peritoneum and therefore a first line with dabrafenib (D)+ trametinib (T) was started at a full dose of 300 mg D and 2 mg T.
- During treatment 2 drug-interruptions due to fever and cutaneous rash and one dose reduction to D 200 mg and T 1,5 mg were needed. Nevertheless, a complete metabolic and dimensional response was achieved after 4 months of treatment, with no further disease progression. D+T was stopped due to patient will and untolerable toxicity (fever >39°C and diffuse cutaneous rash not manageable with steroids).
- In September 2019 a shift to Encorafenib (E)+ Binimetinib (B) was done. B was stopped in March 2020 due to a left kystoid macular oedema with acute visual loss (1/10). Given the persistence of the visual loss and the lack of regression of the ocular toxicity, E was also stopped in September 2020. Nevertheless PET/TC and CT continue to show complete response, which was persistent in June 2022. The ocular toxicity has completely recovered after E+B interruption.



Apr 11 lymph node relapse
Surgery + vemurafenib



Jul 16 Best Response under nivolumab

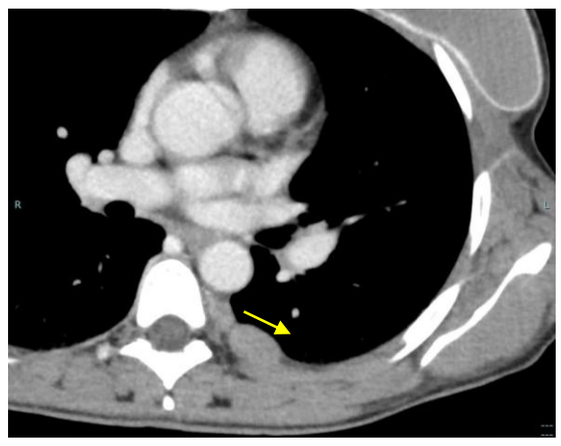


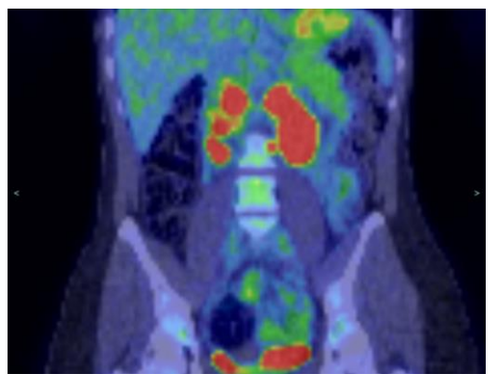
July 18 Retroperitoneal Lymph node relapse. Starts D+T+

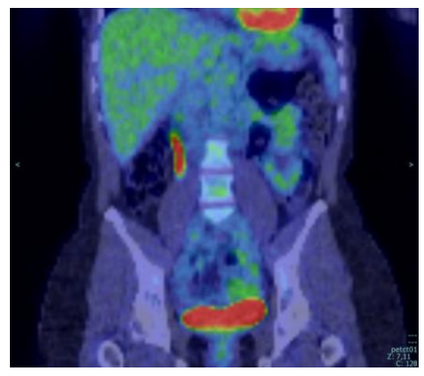
Oct 15 left pleural relapse
Starts nivolumab

July 18 Retroperitoneal Lymph node relapse. Starts D+T+

June 22 CR persistence after > 2 years E+B interruption







Conclusions

The hereby depicted case shows that sustained long term disease control may be achieved and maintained in patients with BRAF V600E mutated melanoma even after long term drug interruptions due to intolerable toxicities.
Further investigation on exceptional responders with severe toxicities is warranted in order to identify potential biomarkers.

AO AL Azienda Ospedaliera di ALESSANDRIA Santi Antonio e Biagio e Cesare Arrigo